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A Randomized Phase II Trial (TAMIGA) Evaluating the Efficacy and Safety of Continuous Bevacizumab Through Multiple Lines of Treatment for Recurrent Glioblastoma

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Clinical trial • Continuous bevacizumab • Overall survival • Recurrent glioblastoma

Abstract

Background. We assessed the efficacy and safety of bevacizumab (BEV) through multiple lines in patients with recurrent glioblastoma who had progressed after first-line treatment with radiotherapy, temozolomide, and BEV.

Patients and Methods. TAMIGA (NCT01860638) was a phase II, randomized, double-blind, placebo-controlled, multicenter trial in adult patients with glioblastoma. Following surgery, patients with newly diagnosed glioblastoma received first-line treatment consisting of radiotherapy plus temozolomide and BEV, followed by six cycles of temozolomide and BEV, then BEV monotherapy until disease progression (PD1). Randomization occurred at PD1 (second line), and patients received lomustine (CCNU) plus BEV (CCNU + BEV) or CCNU plus placebo (CCNU + placebo) until further disease progression (PD2). At PD2 (third line), patients continued BEV or placebo with chemotherapy (investigator's choice). The primary endpoint was survival from randomization. Secondary endpoints were progression-free survival in the second and third lines (PFS2 and PFS3) and safety.

Results. Of the 296 patients enrolled, 123 were randomized at PD1 (CCNU + BEV, n = 61; CCNU + placebo, n = 62). The study was terminated prematurely because of the high dropout rate during first-line treatment, implying underpowered inferential testing. The proportion of patients receiving corticosteroids at randomization was similar (BEV 33%, placebo 31%). For the CCNU + BEV and CCNU + placebo groups, respectively, median survival from randomization was 6.4 versus 5.5 months (stratified hazard ratio [HR], 1.04; 95% confidence interval [CI], 0.69–1.59), median PFS2 was 2.3 versus 1.8 months (stratified HR, 0.70; 95% CI, 0.48–1.00), median PFS3 was 2.0 versus 2.2 months (stratified HR, 0.70; 95% CI, 0.37–1.33), and median time from randomization to a deterioration in health-related quality of life was 1.4 versus 1.3 months (stratified HR, 0.76; 95% CI, 0.52–1.12). The incidence of treatment-related grade 3 to 4 adverse events was 19% (CCNU + BEV) versus 15% (CCNU + placebo).

Conclusion. There was no survival benefit and no detriment observed with continuing BEV through multiple lines in patients with recurrent glioblastoma. ***The Oncologist*** 2019;24:521–528

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Implications for Practice: Previous research suggested that there may be value in continuing bevacizumab (BEV) beyond progression through multiple lines of therapy. No survival benefit was observed with the use of BEV through multiple lines in patients with glioblastoma who had progressed after first-line treatment (radiotherapy + temozolomide + BEV). No new safety concerns arose from the use of BEV through multiple lines of therapy.

Introduction

Glioblastomas account for almost 50% of malignant central nervous system (CNS) tumors and have an annual incidence of 3.2 per 100,000 in the U.S. [1]. Glioblastomas are characterized by overexpression of vascular endothelial growth factor (VEGF)-A (a key tumor-associated regulator of angiogenesis) and a high degree of vascularization. Despite first-line treatment with surgical resection followed by radiotherapy (RT) plus concomitant and adjuvant temozolomide (TMZ) [2, 3], the prognosis remains poor, with 1- and 5-year glioblastoma survival rates of 39.3% and 5.5%, respectively [1]. In the recurrent setting, chemotherapy remains the main treatment option [4]; nitrosourea-based regimens, such as lomustine (CCNU), are the preferred choice [5–8]. The efficacy of chemotherapeutic agents is limited, and there remains a high unmet medical need to establish effective glioblastoma treatments; anti-VEGF agents, such as bevacizumab (BEV), have been investigated.

BEV is approved in more than 60 countries worldwide, including the U.S., for use in adults with recurrent glioblastoma [9–11]. At the time of the protocol conception and initiation, two randomized, phase III trials showed that the addition of BEV to RT and TMZ extended progression-free survival (PFS) in adult patients with newly diagnosed glioblastoma but did not improve overall survival (OS) [12, 13].

Tumors may be less likely to develop resistance to antiangiogenic agents than to chemotherapy [14]. VEGF has been implicated in the acquisition of drug resistance in tumor endothelial cells [15], and resistance to BEV would need to occur through development of alternative angiogenesis pathways. Thus, there may be value in continuing BEV through multiple lines [16–19]. The strategy of sustained VEGF inhibition has been extensively investigated in metastatic colorectal cancer, in which continuing BEV through multiple lines improved OS [16, 17]. A retrospective pooled analysis of five consecutive, single-arm, phase II clinical studies evaluating BEV-based treatments for recurrent glioblastoma suggested that BEV continuation beyond initial progression was an independent predictor of improved OS [19].

The placebo-controlled TAMIGA study aimed to assess the efficacy and safety of BEV through multiple lines (plus CCNU in second line and chemotherapy of investigator's choice in third line and beyond) in patients with glioblastoma who had received first-line treatment with RT, TMZ, and BEV prior to randomization.

Materials and Methods

Study Design

TAMIGA (study number MO28347; ClinicalTrials.gov NCT01860638) was a randomized, double-blind, placebo-controlled, multicenter, phase II trial in patients with recurrent glioblastoma. The study was originally designed as a phase III trial, following the phase III AVAglio study (BEV in newly diagnosed glioblastoma) [12], in which one of the coprimary endpoints (improved PFS with BEV + RT + TMZ vs. placebo + RT + TMZ) was met. However, the other coprimary endpoint (improved OS) was not met, and approval for the BEV indication to include adult patients with newly diagnosed glioblastoma was not granted by the Committee for Medicinal Products for Human Use. Thus, the sponsor amended the TAMIGA design to a phase II trial, stopping recruitment with front-line RT plus TMZ and BEV but allowing already enrolled patients to continue in the study, maintaining the same endpoints as the planned phase III trial.

First-line treatment included RT plus TMZ and BEV, followed by maintenance treatment with six cycles of TMZ plus BEV, then BEV monotherapy until first disease progression (PD1; Fig. 1). At PD1, patients eligible for second-line therapy were randomized 1:1 to receive CCNU + BEV or CCNU + placebo through subsequent lines of treatment until second PD (PD2). The CCNU dose was 90 mg/m^2 (maximum of 160 mg) every 6 weeks, increasing to 110 mg/m^2 (maximum of 200 mg) in the absence of hematologic toxicity grade >1 during the first cycle. The BEV dose was 10 mg/kg every 2 weeks (intravenous). At PD2, patients continued to receive BEV or placebo (according to randomization at PD1) in addition to chemotherapy of investigator's choice. Stratification factors included PD1 timing (before vs. after completion of first-line maintenance therapy) and Eastern Cooperative Oncology Group performance status (ECOG PS, 0 vs. 1 or 2). Investigators and patients were blinded to treatment assignment.

Disease status was assessed by response assessment in neuro-oncology (RANO) criteria [20]. All patients were followed until death, withdrawal of consent, loss to follow-up, or study termination, whichever occurred first. The study end was defined as the date when the last visit of the last patient occurred (planned as 30 days after the 130th OS event was reported, estimated to be approximately 36 months after the first patient enrolled).

The protocol was approved by institutional review boards/ethics committees, and the study was conducted in accordance with individual countries' regulations, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice guidelines, and the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients.

Patients

Patients aged ≥18 years with newly diagnosed glioblastoma histologically confirmed with surgical resection or biopsy, who had not been previously treated with chemotherapy or RT, were enrolled to receive front-line treatment according

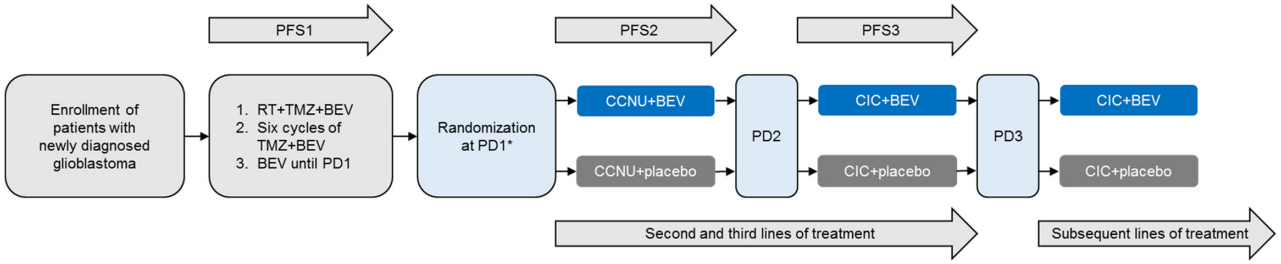

Figure 1. TAMIGA study design. Stratification factors: occurrence of PD1 relative to completion of first-line maintenance therapy (before vs. after completion) and Eastern Cooperative Oncology Group performance status at randomization (0 vs. 1 or 2).
Abbreviations: *, start of TAMIGA study; BEV, bevacizumab; CCNU, lomustine; CIC, chemotherapy (investigator's choice); PD1, first disease progression; PD2, second disease progression; PD3, third disease progression; PFS1, first-line progression-free survival; PFS2, second-line progression-free survival; PFS3, third-line progression-free survival; RT, radiotherapy; TMZ, temozolomide.

to the regimen used in the AVAglio trial [12]. Key exclusion criteria included prior chemotherapy or immunotherapy for glioblastoma or low-grade astrocytoma, or prior RT to the brain; prior or current antiangiogenic treatment; treatment with another investigational agent within 28 days or two investigational agent half-lives (whichever was longer) prior to first study treatment; and history or evidence of CNS disease unrelated to cancer unless adequately treated with standard medical therapy.

At PD1 (by RANO criteria), patients were randomized if they had an ECOG PS of 0–2 and no BEV interruptions lasting >60 consecutive days during first-line treatment. Randomization occurred within 28 days from PD1. Second surgery at PD1 was allowed (no BEV at least ±28 days from surgery). Tissue submission was mandatory before the start of second-line treatment.

Study Assessments

The primary endpoint was OS, defined as the time from randomization at PD1 until death from any cause. Secondary endpoints included 6-, 12-, and 18-month OS rates (as measured from randomization at PD1); PFS in the second (PFS2) and third (PFS3) lines of treatment; corticosteroid use; and health-related quality of life (HRQoL). See supplemental online Appendix 1 for further definitions and details. Exploratory analyses of OS from enrollment and PFS from enrollment (PFS1) were also conducted.

Safety

Patients were monitored throughout the study for adverse events (AEs), serious AEs (SAEs), AEs of special interest (AESIs), and any AEs requiring drug interruption or discontinuation. Safety monitoring was performed every 3–6 months by an independent data monitoring committee.

Statistical Analysis

Full statistical methods are described in supplemental online Appendix 1.

Results

Patients

Overall, 296 patients were enrolled at 51 sites between August 2013 and December 2014. At the clinical cutoff date (January 13, 2017), 54% of patients discontinued first-line treatment with RT + TMZ + BEV, and 123 patients were randomized at PD1 (CCNU + BEV, n = 61; CCNU + placebo, n = 62). Reasons for treatment discontinuation included AEs/SAEs (24.0%), investigator decision (8.1%), withdrawal of patient consent (5.1%), death (4.7%), administrative/other (4.7%), patient decision (4.1%), nonadherence (3.0%), and protocol violation (0.3%). During the second line, 56% of CCNU + BEV-treated patients and 58% of CCNU + placebo-treated patients discontinued study treatment. The most common reasons for treatment discontinuation in the CCNU + BEV and CCNU + placebo groups included investigator decision (16% and 18%), SAEs (10% and 13%), and withdrawal of patient consent (7% and 10%). At PD2, 25 patients in each group received third-line treatment (supplemental online Fig. 1).

Patient characteristics at randomization were balanced between the treatment groups (Table 1), although more patients in the CCNU + BEV group were in recursive partitioning analysis class III than those in the CCNU + placebo group (20% and 8%, respectively). The majority of patients did not undergo reoperation at PD1 (CCNU + BEV, 92%; CCNU + placebo, 95%). Both treatment arms had a similar number of patients with (un-)methylated O6-methylguanine-DNA methyltransferase. Gene expression profiling is currently ongoing (supplemental online Appendix 1).

Exposure to BEV or Placebo

Among patients randomized to receive second-line treatment, the median number of total administrations per patient was 4.0 (range, 1–17) and 3.0 (range, 1–35) in the CCNU + BEV and CCNU + placebo groups, respectively, and 81% and 80% of patients completed ≥90% of planned doses. Corresponding median values among patients who received third-line treatment were 4.0 (range, 1–12) and 4.0 (range, 1–58) administrations, with 100% and 88% of patients completing ≥90% of planned doses.

A summary of the exposure to treatment in second and subsequent lines is shown in supplemental online Table 1.

OS (Primary Endpoint)

The study was terminated prematurely because of a high drop-out rate during first-line treatment, implying underpowered (i.e., 60%) inferential testing; only 98 of the targeted 130 OS events for the primary endpoint were reached in the 123 randomized patients; therefore, no p values are reported and only 95% confidence intervals (CIs) are shown.

Table 1. Patient demographics and clinical characteristics at randomization (intent-to-treat population)

Patient characteristics	CCNU + placebo group (*n* = 62), *n* (%)	CCNU + BEV group (*n* = 61), *n* (%)	Total (*n* = 123), *n* (%)
Age, median (range), years	58.5 (36–74)	56.0 (30–74)	56.0 (30–74)
Male	45 (73)	44 (72)	89 (72)
KPS			
100	11 (18)	16 (26)	27 (22)
90	21 (34)	17 (28)	38 (31)
80	16 (26)	12 (20)	28 (23)
70	8 (13)	11 (18)	19 (15)
60	5 (8)	5 (8)	10 (8)
50	1 (2)	0	1 (1)
ECOG PS			
0	24 (39)	26 (43)	50 (41)
1	27 (44)	23 (38)	50 (41)
2	11 (18)	12 (20)	23 (19)
MMSE total score			
<27	12 (19)	16 (26)	28 (23)
≥27	25 (40)	24 (39)	49 (40)
Missing	25 (40)	21 (34)	46 (37)
RPA class			
III	5 (8)	12 (20)	17 (14)
IV	14 (23)	8 (13)	22 (18)
V	9 (15)	9 (15)	18 (15)
Missing	34 (55)	32 (52)	66 (54)
Occurrence of PD1 relative to completion of first-line maintenance therapy			
Before completion	16 (26)	14 (23)	30 (24)
After completion	46 (74)	47 (77)	93 (76)
Corticosteroid use			
Yes	19 (31)	20 (33)	39 (32)
No	43 (69)	41 (67)	84 (68)
Operation or reoperation of glioblastoma at PD1			
Yes	3 (5)	5 (8)	8 (7)
No	59 (95)	56 (92)	115 (93)
MGMT status[a]			
Unmethylated	25	26	51
Methylated	12	11	23

[a]Not all randomized patients had a valid MGMT status result.
Abbreviations: BEV, bevacizumab; CCNU, lomustine; ECOG PS, Eastern Cooperative Oncology Group performance status; KPS, Karnofsky performance status; MGMT, methylated O6-methylguanine-DNA methyltransferase; MMSE, Mini-Mental State Examination; PD1, first disease progression; RPA, recursive partitioning analysis.

In the intent-to-treat population, median OS from randomization was 6.4 (95% CI, 5.1–8.1) and 5.5 months (95% CI, 3.9–7.2) in the CCNU + BEV and CCNU + placebo groups, respectively (stratified hazard ratio [HR], 1.04; 95% CI, 0.69–1.59; Fig. 2). The OS for the per protocol population (sensitivity analysis) showed comparable results (median 6.0 and 4.9 months, respectively; HR, 1.01; 95% CI, 0.62–1.64).

OS Rates and PFS (Secondary Endpoints)

The Kaplan-Meier-estimated event-free rates (CCNU + BEV vs. CCNU + placebo, respectively) for OS at 6, 12, and 18 months were 55.4% (95% CI, 41.4–67.3) versus 46.2% (95% CI, 32.8–58.5), 11.7% (95% CI, 4.6–22.5) versus 16.5% (95% CI, 7.5–28.5), and 4.7% (95% CI, 0.9–13.7) versus 9.4% (95% CI, 3.1–20.1). For CCNU + BEV versus CCNU + placebo, respectively, values for median PFS2 were 2.3 months (95% CI, 1.9–2.7) and 1.8 months (95% CI, 1.4–2.1; stratified HR, 0.70; 95% CI, 0.48–1.04; Fig. 3A), and median PFS3 was 2.0 months (95% CI, 1.8–2.7) and 2.2 months (95% CI, 1.3–2.7, stratified HR, 0.70; 95% CI, 0.37–1.33; Fig. 3B). Definitions of PFS2 and PFS3 are described in supplemental online Appendix 1.

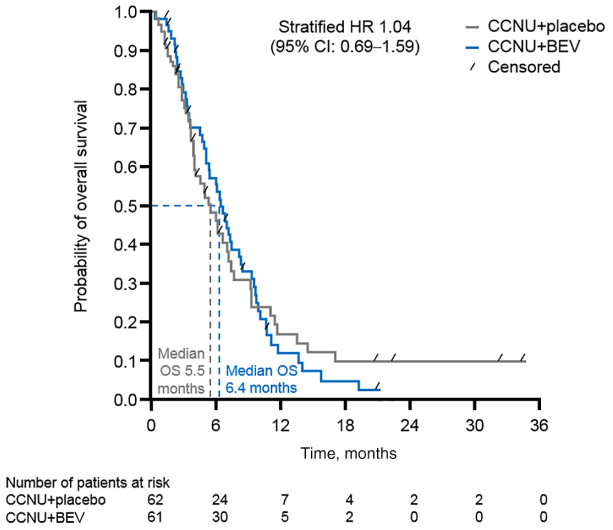

Figure 2. OS from randomization with multiple-line BEV treatment versus placebo (primary efficacy endpoint).
Abbreviations: BEV, bevacizumab; CCNU, lomustine; CI, confidence interval; HR, hazard ratio; OS, overall survival.

Corticosteroid Intake

The proportion of patients receiving corticosteroids at the time of randomization was balanced between treatment arms (33% vs. 31%, CCNU + BEV vs. CCNU + placebo, respectively). For those patients not receiving corticosteroids at the time of randomization (BEV, *n* = 41; placebo, *n* = 43), the median time from randomization to corticosteroid initiation during second-line treatment was 5.8 months (95% CI, 2.3–13.7) in the CCNU + BEV group, and 5.4 months (95% CI, 3.5–9.3) in the CCNU + placebo group (unstratified HR, 1.05; 95% CI, 0.59–1.87; Fig. 4).

Analyses of OS from Enrollment and PFS from Enrollment (PFS1; Exploratory Analyses)

Median OS from enrollment, at time of diagnosis, was 18.1 (95% CI, 13.9–20.7) and 16.4 months (95% CI, 14.3–20.3) in the CCNU + BEV and CCNU + placebo groups, respectively (supplemental online Fig. 2). Median PFS1 was 10.8 months (95% CI, 10.3–11.8).

Safety and HRQoL

Across the second and third lines of treatment combined, in the CCNU + BEV and CCNU + placebo groups, respectively, 86% and 83% of patients experienced at least one AE, 19% and 15% experienced at least one treatment-related grade ≥3 AE, 20% and 9% experienced at least one SAE, 21% and 15% experienced an AE leading to study discontinuation, and 69% and 56% had at least one AESI (Table 2). More patients in the CCNU + BEV group experienced thrombocytopenia (mostly grade 1–2) than those receiving CCNU + placebo (48% vs. 29%).

A similar number of patients died during the study in the CCNU + BEV (*n* = 42 [67%]) and CCNU + placebo (*n* = 41 [70%]) groups, with the majority of deaths in both treatment groups due to disease progression (41 of 42 [98%] and 39 of 41 [95%], respectively). None of the deaths was considered treatment related.

Analysis of median time to HRQoL deterioration in second-line treatment did not show a difference between the treatment groups: 1.3 months (95% CI, 1.0–1.6) in the CCNU + placebo group and 1.4 months (95% CI, 1.2–2.0) in the CCNU + BEV group (stratified HR, 0.76, 95% CI, 0.52–1.12; supplemental online Fig. 3).

Discussion

Although this study was initially designed as a phase III study, the protocol was amended, and the design was changed to a phase II study with the same primary endpoint (OS). There was no observed benefit or detrimental effect on OS with the addition of BEV to second-line CCNU and third-line chemotherapy of investigator's choice in patients with recurrent glioblastoma; however, PFS2 was numerically longer with CCNU + BEV than with CCNU + placebo (although PFS3 was not).

Overall, these findings are in line with previous studies of BEV for newly diagnosed glioblastoma, in which improvements in PFS with the addition of BEV to RT and TMZ did not translate to an OS benefit [16, 17]. A recent meta-analysis showed that BEV improved PFS, both alone and in combination with chemotherapy, and both as first-line treatment or in recurrent glioblastoma, but no improvement in OS was observed [21]. The median OS of 6.4 months for BEV-treated patients in the current study was shorter than that reported in a previous phase II trial of BEV at first recurrence (9 months) [14]; however, in that study (the BRAIN study), patients had no prior exposure to BEV. Median PFS1 and OS from enrollment in the current study (10.8 months and 18.1 months, respectively) are consistent with the PFS and OS observed in the AVAglio study (10.6 months and 16.8 months, respectively) [12]. The lack of OS benefit observed in the current study is also consistent with the European Organisation for Research and Treatment of Cancer 26101 trial of CCNU plus BEV versus CCNU alone for recurrent glioblastoma (median OS 9.1 vs. 8.6 months) [22].

A previous study of BEV through multiple lines (TML) for the treatment of patients with metastatic colorectal cancer who had progressed following first-line BEV-based therapy showed an OS benefit compared with second-line chemotherapy alone (median OS 11.2 vs. 9.8 months; HR, 0.81; 95% CI, 0.69–0.94; p = .006) [12]. However, there is limited existing literature, mainly retrospective with relatively small study samples, on the efficacy of BEV through multiple lines for patients with glioblastoma. One retrospective study of patients with recurrent malignant glioma showed that continuing BEV and modifying the chemotherapy agent after disease progression only provided long-term control in a small subset of patients [23]. Other studies have suggested that BEV continuation beyond initial progression was an independent predictor of improved OS in patients with recurrent glioblastoma [19]. The prospective phase II CABARET study of patients with recurrent glioblastoma who progressed on BEV did not demonstrate improvements in median PFS or OS with continuing BEV beyond disease progression compared with stopping BEV treatment [24].

In the current study, the proportion of patients who were receiving corticosteroids at randomization was similar

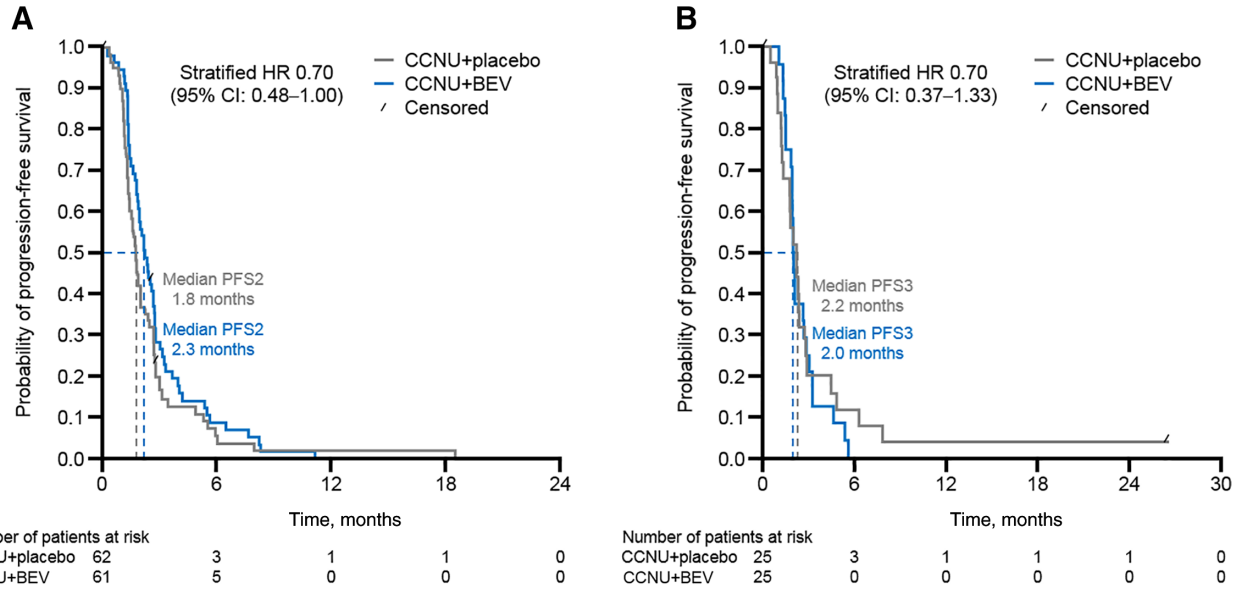

Figure 3. PFS2 and PFS3 with multiple-line BEV treatment versus placebo. **(A):** PFS2. **(B):** PFS3.
Abbreviations: BEV, bevacizumab; CCNU, lomustine; CI, confidence interval; HR, hazard ratio; PFS2, second-line progression-free survival; PFS3, third-line progression-free survival.

between treatment groups (approximately one third) and lower than the proportion of patients using corticosteroids reported at study entry in previous trials of recurrent glioblastoma (49%–54%) [14, 15, 22]. This may suggest that patients who received first-line BEV in addition to RT and TMZ benefitted in terms of reduced corticosteroid use. This is in line with the AVaglio study, in which more patients with newly diagnosed glioblastoma were able to discontinue corticosteroid use for ≥5 consecutive days in the BEV + RT + TMZ arm, versus placebo plus RT + TMZ (66.3% vs. 47.1%) [16]. In TAMIGA, there were no differences between treatment groups in the time of initiation and use of corticosteroids after randomization. Time-to-event analysis of HRQoL deterioration in second-line treatment did not show a difference between the placebo and BEV groups (supplemental online Appendix 1), which is consistent with previous trials [22, 24].

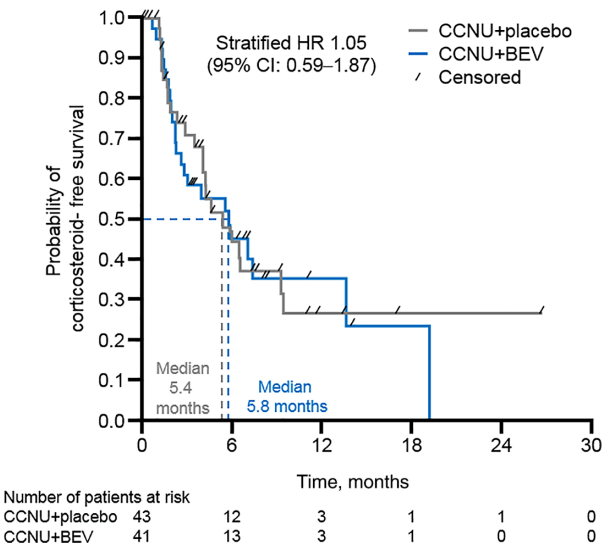

Figure 4. Time-to-event analysis of corticosteroid initiation in second-line treatment with BEV versus placebo. A deterioration in health-related quality of life (HRQoL) was defined as a decrease of ≥10 points from randomization on the respective functional scale/global health status or an increase of ≥10 points from randomization on the respective symptom/neurological deficit subscales; time to HRQoL deterioration was defined as the time from randomization to HRQoL deterioration or second-line progression or death due to any cause.
Abbreviations: BEV, bevacizumab; CCNU, lomustine; CI, confidence interval; HR, hazard ratio.

Administration of BEV through multiple lines may raise concerns about increased toxicity; this was addressed by comparing BEV through multiple lines to a placebo-treated control arm. No new safety signals were observed. The incidence of AEs in second and third lines of treatment was generally similar between the treatment groups, although the incidence of SAEs in second-line treatment was higher with CCNU + BEV than with CCNU + placebo (18% vs. 7%). The higher rate of thrombocytopenia observed in the CCNU + BEV group than in the CCNU + placebo group is in line with data from the BELOB and AVAREG studies [6, 7]. The high rates of study treatment discontinuation in second and third lines of treatment observed in this study reflect the hastened clinical deterioration upon progression and the difficulty in managing these patients in clinical practice. Similarly, in the CABARET trial, only 40% of patients who were initially randomized to receive BEV were able to continue into the second part of the study after further disease progression (80% of the planned sample size) [24].

A strength of this study is that we evaluated the efficacy and safety of BEV through multiple lines of therapy in patients with recurrent glioblastoma with a placebo-controlled design in all subsequent lines of chemotherapy. The design was intended to provide a representative comparison to the treatment path of patients with glioblastoma throughout the course of the disease and to minimize the confounding factor

Table 2. Overview of safety in second- and third-line treatments (safety population)

Category	CCNU + placebo (*n* = 59), *n* (%)	CCNU + BEV (*n* = 63), *n* (%)
Any AEs	49 (83)	54 (86)
Any treatment-related AEs	30 (51)	34 (54)
Any treatment-related grade ≥3 AEs	9 (15)	12 (19)
Number of patients with any SAEs in second- or third-line treatment	5 (9)	12 (20)
Total number of SAEs in second-line treatment[a]	4	16
Any AEs leading to study discontinuation	9 (15)	13 (21)
Any AEs leading to discontinuation of BEV	7 (12)	7 (11)
Any AESIs in second- or third-line treatment	33 (56)	43 (69)
Any AESIs in second-line treatment	30 (51)	42 (67)
Bleeding (all grades)	6 (10)	4 (6)
Gastrointestinal perforation (grade ≥3)	1 (2)	0
Hypertension (all grades/grade ≥3)	14 (24)/7 (12)	19 (30)/9 (14)
Proteinuria (all grades/grade ≥3)	9 (15)/0	11 (18)/2 (3)
Thrombocytopenia (all grades)	17 (29)	30 (48)
Thrombocytopenia (grade ≥3)	5 (9)	3 (5)
Decreased platelet count (grade ≥3)	5 (9)	7 (11)
Thromboembolic events (all grades/grade ≥3)	3 (5)/1 (2)	5 (8)/2 (3)
Wound-healing complications (all grades)	1 (2)	1 (2)

Preferred terms used as reported.

[a]A number of patients experienced more than one SAE. CCNU + placebo: decreased platelet count, thrombocytopenia, large intestine perforation, and allergic dermatitis (*n* = 1 [2%] each); CCNU + BEV: seizure (*n* = 3 [5%]); pulmonary embolism (*n* = 2 [15%]); aphasia, transverse myelitis, subdural effusion, diarrhea, diverticulum, increased gamma-glutamyl transpeptidase, pneumonia, hand fracture, decreased platelet count, and thrombocytopenia (*n* = 1 [2%] each).

Abbreviations: AE, adverse event; AESI, AEs of special interest; BEV, bevacizumab; CCNU, lomustine; SAE, serious adverse event.

of crossover from the placebo arm in later lines. Limitations include the high rate of study treatment discontinuation during first and second lines of treatment, which led to the premature termination of the study, limiting our ability to draw strong conclusions regarding treatment effects.

Conclusion

This study was terminated prematurely and was underpowered to address the primary objective. Descriptive analyses showed that there was no benefit or detriment in OS with continuing multiple-line BEV treatment in patients with glioblastoma who had progressed following first-line treatment with RT, TMZ, and BEV. No new safety signals were observed with BEV through multiple lines.

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Disclosures

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